

## **II. REMARKS**

Claims 1-27 are pending and stand variously rejected under 35 U.S.C. §§ 112, second paragraph; 102; and 103.

The specification has been amended herein to correct a typographical error. Claim 1 has been amended to clarify that the HCV E2 antigen encoded by the polynucleotide is full-length and, in addition, that the HCV antigen encoded by the administered polynucleotide is not secreted when expressed in the subject's cells. Support for the amendments to claim 1 can be found throughout the specification as filed, for example on page 17, lines 1-5. Claim 7 has been amended to clarify that the recited amino acid residues are numbered relative to HCV-1, for example as described on page 16, lines 19 and 24-25. Dependent claims 4-6, 8-12, 14, 16, 17, 26 and 27 have been amended to be multiply dependent. The amendments are made solely to expedite prosecution, are not intended in any way as an acknowledgment as to the correctness of the Examiner's position.

In view of the foregoing amendments and following remarks, reconsideration of the claims is respectfully requested.

### **35 U.S.C. § 112, Second Paragraph**

Claims 1-27 stand variously rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Specifically, it is alleged that the steps of claim 1 are not clear and that the phrases following the whereins on lines 3 and 4 are vague and indefinite. (Office Action, page 2). Claim 3 is alleged to be indefinite in their recitation "neutralizing of binding antibodies." (Office Action, page 2). Claim 6 is alleged to be indefinite in reciting "p7." (Office Action, page 2). Finally, claim 7 is alleged to be indefinite in failing to refer to something that defined the specific amino acid residues. (Office Action, page 2). Applicants address each issue in turn.

The rejection of the claim 1 has been overcome by the foregoing amendments

which clarify the steps of the claims and the nature of the compositions used in the claimed methods.

With regard to claim 3, Applicants note that the term “neutralization of binding antibody” is clearly defined in the specification and in the art to refer to an antibody that neutralizes (*e.g.*, blocks) binding of viral particles to host cells. (See, *e.g.*, page 2, lines 16-18 of the specification and Immunology, Kubly et al. page 427, copy attached hereto). In view of the clear description of this term in the specification and understanding of NOB antibodies in the field, Applicants submit that claim 3 is not indefinite or vague.

Similarly, with regard to the recitation of the term “p7” in claim 6, Applicants direct the Examiner’s attention to page 16, line 17-19 of the specification where it is clearly indicated that p7 is an HCV protein found between E2 and NS2 in an HCV polyprotein and, additionally, that E2 extends to approximately amino acid residue 746, numbered relative to HCV-1. Thus, p7 necessarily begins at approximately amino acid residue 747 (numbered relative to HCV-1) and extends to the beginning of NS-2. Furthermore, it was well-known in the art at the time of the specification was filed that HCV p7 was a 63 amino acid protein extending from amino acid residue 747 to 809 (numbered relative to HCV-1). (See, Abstract by Lin et al. attached hereto). Thus, the metes and bounds of an HCV p7 protein are clear from both the specification as filed and state of the art at the time of filing.

Finally, turning to claim 7, Applicants submit that the foregoing amendments obviate this rejection inasmuch as this claim now indicates that the amino acid residues recited in the claims are numbered relative to HCV-1. The entire sequence of HCV-1 was known at the time of filing. (See, *e.g.*, page 16, line 19 of the specification citing Choo et al which contains the entire HCV-1 polyprotein sequence).

In view of the foregoing amendments and remarks, Applicants submit that the rejections have been obviated or otherwise overcome and, accordingly, request that the rejections under Section 112, second paragraph be withdrawn.

**35 U.S.C. § 102**

Claims 1-6, 8, 9 and 12-15 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,306,405 (hereinafter “O’Hagan”). In addition, claims 1, 2, 4, 5, 9, 10, 26 and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wyatt et al. (1998) *J. Virol.* 72(3):1725-1730 (hereinafter “Wyatt”). It is alleged that O’Hagan discloses the use of HCV E2 as a DNA immunogen using microparticles to raise an immune response. (Office Action, page 3). Wyatt is cited for allegedly teaching that an immune response is elicited in chimpanzees by administration of a polynucleotide encoding a full-length E1/E2 polypeptide. (Office Action, page 3).

Applicants traverse the rejections and supporting remarks.

In order to be an anticipatory reference, the single reference cited by the Office must disclose each and every element of the claims. *See, e.g., Hybritech v. Monoclonal Antibodies*, 231 USPQ 81 (Fed. Cir. 1986). Moreover, the single source must disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989).

The pending claims are directed to methods of generating an immune response against an HCV antigen by administering a polynucleotide encoding E2 or E1E2 to a subject. Neither O’Hagan nor Wyatt disclose such methods. In particular, O’Hagan discloses compositions comprising a polypeptide antigen and microparticles in combination with oil-in-water emulsions. (See, Abstract and Examples of O’Hagan). For its part, Wyatt fails to disclose administration of any polynucleotides to chimpanzees. Instead, Wyatt is directed to sequencing of clones of HVR1 obtained from chimpanzees infected with whole HCV-H virus. Simply put, there is no description or demonstration in either O’Hagan or Wyatt regarding methods involving administration of polynucleotides encoding HCV antigens and, according, the pending claims are not anticipated by either references. Therefore, Applicants respectfully request that these

rejections be withdrawn.

**35 U.S.C. § 103**

Claims 10, 11 and 16-27 stand rejected under 35 U.S.C. section 103(a) as allegedly obvious over O'Hagan. Briefly stated, the Office maintains that the use of cardiotoxin with DNA administration was known and that it would have been obvious to one skilled in the art to modify "the immunogen of O'Hagan with techniques known in the art to improve the results with the expectation of success." (Office Action, page 4).

For the reasons noted above, Applicants submit that O'Hagan fails to teach or suggest administration of polynucleotides encoding HCV E2 or E1E2 antigens to generate an immune response. Thus, the Office has not pointed to anything in O'Hagan that would lead one of skill in the art to combine cardiotoxin delivery with administration of polynucleotides encoding HCV E1E2 or full-length HCV E2 antigens, as claimed. Accordingly, the Office has not established a *prima facie* case of obviousness and withdrawal of these rejections is respectfully requested.

**III. CONCLUSION**

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

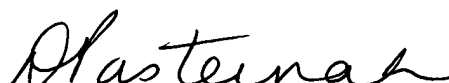
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**Version Showing Changes Made to the Specification**

The paragraph beginning on line 19, page 2 has been amended as follows:

--Thus, in one aspect, the invention includes a method of eliciting an immune response against a hepatitis C virus (HCV) E2 and/or E1E2 antigen (*e.g.*, one or more purified polynucleotides encoding these antigens) comprising the step of (a) administering to a subject at least one polynucleotide encoding the E2 and/or E1E2 antigen(s). The polynucleotides encode HCV E2 and/or E1E2 polypeptides that are preferably non-secreted and, additionally, encode full-length E2. In preferred embodiments, the immune response is a humoral immune response, for example, a response that generates at least one neutralization of binding (NOB) antibody. In certain embodiments, more than one polynucleotide encoding different E2 or E1E2 antigens are administered. In various embodiments, the full-length (or non-truncated) E2 antigen(s) encoded by the polynucleotide(s) comprise/comprises amino acids 384-746 of an HCV polyprotein; amino acids 384-749 of an HCV polyprotein; 384-809 of an HCV polyprotein; or combinations thereof. In other embodiments, the antigen(s) encoded by the polynucleotide(s) include/includes E1 as well as E2 (*e.g.*, constructs encoding amino acids 192-746 of an HCV polyprotein, amino acids 192-809 of an HCV polyprotein; amino acids 192-749 of an HCV polyprotein). Thus, the polynucleotides may encode one or more full-length E2 and one or more E1E2 antigens. In further embodiments, the antigen(s) is/are intracellularly produced (*e.g.*, not secreted) truncated E2 (*e.g.*, amino acids 384-715 of an HCV polyprotein; amino acids 384-661 of an HCV polyprotein, amino acids 340-674 of an HCV polyprotein). The polynucleotides may be, for example, DNA, plasmid DNA or other expression vector. In any of the methods described herein, the subject is or is not infected with one or more strains of HCV. Furthermore, in various embodiments, the methods may further comprise the step of administering an adjuvant (*e.g.*, cardiotoxin) to the mammal.--

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**Version Showing Changes Made to the Claims**

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1. (Amended) A method of eliciting an immune response against a hepatitis C virus (HCV) E2 or E1E2 antigen comprising the step of (a) administering to a subject a polynucleotide encoding [the E2 or] an HCV E1E2 antigen or a full-length E2 antigen, wherein the E2 [and] or E1E2 antigen encoded by the polynucleotide is not secreted [and wherein E2 is full-length] when expressed in cells of the subject.

4. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the polynucleotide encodes an E1E2 polypeptide.

5. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the polynucleotide encodes a full-length E2 polypeptide.

6. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the HCV antigen does not comprise a p7 polypeptide.

7. (Amended) The method of claim 1, wherein the HCV antigen encoded by the polynucleotide is selected from the group consisting of amino acids 384-746 of an HCV polyprotein; amino acids 384-749 of an HCV polyprotein; amino acids 192-746 of an HCV polyprotein, amino acids 192-809 of an HCV polyprotein; amino acids 192-749 of an HCV polyprotein; and amino acids 384-809 of an HCV polyprotein, wherein the amino acids are numbered relative to HCV-1.

8. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the polynucleotide is in a plasmid.

9. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the subject is infected with an HCV.

10. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the subject is not infected with an HCV.

11. (Amended) The method of [claim 1] claims 1-3 or claim 7, further comprising the step of administering cardiotoxin to the subject.

12. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the polynucleotide is administered using a microparticle.

14. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the

subject is a mammal.

16. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the polynucleotide is administered using a biolistic delivery device.

17. (Amended) The method of [claim 1] claims 1-3 or claim 7, wherein the polynucleotide is administered by a method selected from the group consisting of intramuscular, subcutaneous, intraperitoneal, intranasal, oral, and intradermal administration.

26. (Amended) The method of [claim 1] claims 1-3 or claim 7, further comprising repeating step (a).

27. (Amended) The method of [claim 1] claims 1-3 or claim 7, further comprising administering to the subject a polypeptide encoded by the polynucleotide.



### **Currently Pending Claims**

1. (Amended) A method of eliciting an immune response against a hepatitis C virus (HCV) E2 or E1E2 antigen comprising the step of (a) administering to a subject a polynucleotide encoding an HCV E1E2 antigen or a full-length E2 antigen, wherein the E2 or E1E2 antigen encoded by the polynucleotide is not secreted when expressed in cells of the subject.

2. The method of claim 1, wherein the immune response is a humoral immune response.

3. The method of claim 2, wherein the humoral immune response generates at least one neutralization of binding (NOB) antibody.

4. (Amended) The method of claims 1-3 or claim 7, wherein the polynucleotide encodes an E1E2 polypeptide.

5. (Amended) The method of claims 1-3 or claim 7, wherein the polynucleotide encodes a full-length E2 polypeptide.

6. (Amended) The method of claims 1-3 or claim 7, wherein the HCV antigen does not comprise a p7 polypeptide.

7. (Amended) The method of claim 1, wherein the HCV antigen encoded by the polynucleotide is selected from the group consisting of amino acids 384-746 of an HCV polyprotein; amino acids 384-749 of an HCV polyprotein; amino acids 192-746 of an HCV polyprotein, amino acids 192-809 of an HCV polyprotein; amino acids 192-749 of an HCV polyprotein; and amino acids 384-809 of an HCV polyprotein, wherein the amino acids are numbered relative to HCV-1.

8. (Amended) The method of claims 1-3 or claim 7, wherein the polynucleotide is in a plasmid.

9. (Amended) The method of claims 1-3 or claim 7, wherein the subject is infected with an HCV.

10. (Amended) The method of claims 1-3 or claim 7, wherein the subject is not infected with an HCV.

11. (Amended) The method of claims 1-3 or claim 7, further comprising the step of administering cardiotoxin to the subject.

12. (Amended) The method of claims 1-3 or claim 7,, wherein the polynucleotide is administered using a microparticle.

13. The method of claim 12, wherein the microparticle is a PLG microparticle.

14. (Amended) The method of claims 1-3 or claim 7, wherein the subject is a mammal.

15. The method of claim 14, wherein the mammal is selected from the group consisting of a mouse, a rabbit, a guinea pig, a macaque, a baboon, a chimpanzee, and a human.

16. (Amended) The method of claims 1-3 or claim 7, wherein the polynucleotide is administered using a biolistic delivery device.

17. (Amended) The method of claims 1-3 or claim 7, wherein the polynucleotide is administered by a method selected from the group consisting of intramuscular, subcutaneous, intraperitoneal, intranasal, oral, and intradermal administration.

18. The method of claim 3, wherein the neutralizing of binding antibody inhibits binding of an E2 polypeptide to its cognate receptor by an amount which is greater relative to binding of the E2 polypeptide to its cognate receptor in the absence of the neutralizing of binding antibody.

19. The method of claim 3, further comprising the step of detecting the neutralizing of binding antibody.

20. The method of claim 3, wherein the neutralizing of binding antibody inhibits binding of the E2 polypeptide by at least 50% at a dilution of at least 1:70.

21. The method of claim 3, wherein the neutralizing of binding antibody inhibits binding of the E2 polypeptide by at least 50% at a dilution of at least 1:140.

22. The method of claim 3, wherein the neutralizing of binding antibody inhibits binding of the E2 polypeptide by at least 50% at a dilution of at least 1:300.

23. The method of claim 3 wherein the neutralizing of binding antibody

inhibits binding of the E2 polypeptide by at least 50% at a dilution of at least 1:600.

24. The method of claim 3, wherein the neutralizing of binding antibody inhibits binding of the E2 polypeptide by at least 50% at a dilution of at least 1:800.

25. The method of claim 3, wherein the neutralizing of binding antibody inhibits binding of the E2 polypeptide by at least 50% at a dilution of at least 1:3,000.

26. (Amended) The method of claims 1-3 or claim 7, further comprising repeating step (a).

27. (Amended) The method of claims 1-3 or claim 7, further comprising administering to the subject a polypeptide encoded by the polynucleotide.